Medical Staff Conference

Meningitis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

EDITORS' NOTE: *Although the discussions that usually appear in this section are edited transcripts of the weekly staff conference at the Moffitt-Long Hospitals of the University of California, San Francisco, this discussion represents a fusion of two conferences on the same topic, one given by Dr Merle A. Sande, Professor and Vice-Chairman of the Department of Medicine and Chief of the Medical Service at San Francisco General Hospital Medical Center, and the other given by Dr Lawrence M. Tierney, Jr, Associate Professor of Medicine and Assistant Chief of the Medical Service at the Veterans Administration Medical Center in San Francisco. The editors thank them for their readiness to collaborate in preparing this discussion.*

In this article we discuss the pathophysiology of bacterial meningitis, review briefly the clinical and laboratory features and summarize the current recommended treatment for it. Essential to a successful outcome in this disease is early recognition of the infection because once it has progressed to a critical point, the use of antimicrobial agents is futile. Therapy aimed at the most likely pathogens must be initiated immediately, and antibiotics that achieve bactericidal activity at the site of the infection, which in meningitis is the cerebrospinal fluid (CSF), must be used. Finally, meticulous attention to the details of recognizing and treating complications is also essential for a successful treatment outcome.

Etiology

Recent epidemiologic studies indicate an incidence of about ten new cases of bacterial meningitis per million population yearly in the United States, meaning a total of about 20,000 to 25,000 nationwide. This estimate substantially exceeds the number reported to public health officials. Of the total, roughly three fourths occur in children younger than 12 years of age and the cause is highly dependent on age. Enterobacteriaceae—particularly *Escherichia coli*—and group B *Streptococcus* account for most cases in the neonatal period. In children younger than 6 years of age the encapsulated type B *Hemophilus influenzae* accounts for most cases (about 8,000 a year). Meningococcal meningitis is also more common in children than adults and accounts for 3,000 to 4,000 cases annually. *Streptococcus pneumoniae* can be seen in any age group, but becomes the most common cause of bacterial meningitis in older patients and results in an estimated 6,000 cases per year. *Staphylococcus aureus* is an unusual cause of primary meningitis; however, it is often found in patients with staphylococcal endocarditis. Aerobic Gram-negative bacilli other than *Hemophilus* are rare causes of community-acquired meningitis, but are etiologic with increasing frequency as a complication of a neurosurgical procedure or head trauma. *Listeria monocytogenes* is an organism that can produce meningitis in any age group; although historically associated with patients who have impaired cellular immune responses, it should not be overlooked as a potential pathogen without identified underlying defects in host defenses. *Mycobacterium tuberculosis* must also be remembered as a cause of acute meningitis, particularly in urban areas with large immigrant populations.

Pathophysiology

As a general rule, the brain is well protected from infection. The dura and skull are major local deterrents, and the cranial epidural and subdural spaces are quite inaccessible to blood-borne infection, owing in part to the tight junction capillaries of the blood-brain barrier. Nonetheless, bacteremia is assumed to be a major mechanism in pathogenesis. Likewise, direct entry of organisms into the brain, as in neurosurgery, congenital ectodermal defects, head trauma and complicated sinusitis or otitis (or both), provides a ready explanation for the source of this infection. In light of recent cases of pneumococcal meningitis at the University of California, San Francisco, hospitals, and because it represents a well-understood example of the two most common pathogenetic mechanisms in this disease, it will be discussed here in more detail.

S pneumoniae is a common organism of normal

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ABBREVIATIONS USED IN TEXT
CSF = cerebrospinal fluid
PMNs = polymorphonuclear leukocytes

nasopharyngeal flora in humans. Carriage rates are highest in children of preschool and grade-school ages (20% to 40%).[1] It is therefore not surprising that adults without children (except those with chronic obstructive pulmonary disease and bronchitis) have a very low carriage rate (less than 5%), contrasting with that of adults with young children (15% to 20%). There is evidence to suggest that the organism is spread from person to person during rhinovirus colds.[2] As noted above, and as for other types of meningitis, the bacterium may reach the cerebrospinal fluid either by direct extension from the nasopharynx or by hematogenous dissemination. The direct extension may take place through the cribriform plate and may be associated with sinusitis, otitis or mastoiditis; similarly, the pneumococcus is the commonest cause of meningitis in patients with CSF rhinorrhea after head trauma. As for hematogenous dissemination, it probably occurs in the early period after acquisition of the organism in the nasopharynx because a specific anticapsular antibody appears during an eight-week period of nasopharyngeal carriage of the organism even in patients without clinical pneumococcal infection.[2] Patients who have anticapsular or bactericidal antibodies are protected from the development of meningitis caused by *H influenzae* and *Neisseria meningitidis*.[3-5] Similar studies have not been done with the pneumococcus, due in part to the lack of a well-defined patient population. It is well known, however, that anticapsular antibodies facilitate clearance of the pneumococcus from the blood stream and also reduce the incidence of other invasive diseases such as pneumonia.[6] Dissemination leading to meningitis probably occurs primarily through the pulmonary parenchyma, but a pharyngeal origin cannot be ruled out.

Once the organism gains access to the blood stream, its thick polysaccharide capsule helps it evade phagocytosis by macrophages and polymorphonuclear leukocytes (PMNs). There are, however, several lines of defense that aid a host in overcoming this antiphagocytic effect and thus accelerate the clearance of the organisms.[6] One involves direct activation of the alternate pathway of the complement cascade by the capsular polysaccharide of many pneumococcal serotypes.[7] This results in cleavage of C3 and attachment of C3b to the capsule of the pneumococci and produces opsonic activity that facilitates phagocytosis and clearance of the organism by the reticuloendothelial system. In patients with sickle cell disease[8] or the nephrotic syndrome, components of the alternate pathway of the complement cascade (factor B, C3 proactivator) may be deficient. Such a deficiency leads to impaired opsonization and subsequent failure to clear the organism efficiently. A second line of defense operates in patients with a preexisting anticapsular antibody. The combination of either IgG or IgM coupled with activation of the classical complement cascade results in opsonization of the the polysaccharide capsule, again leading to phagocytosis and clearance of the circulating bacteria. The liver appears to be chiefly responsible for clearing well-opsonized pneumococci, whereas the spleen represents a backup organ for removal of highly virulent or poorly opsonized organisms. One can, therefore, appreciate the need to immunize patients without functioning spleens with Pneumovax, a vaccine containing capsular polysaccharide antigen from 14 of the most common pneumococcal serotypes. Immunization results in circulating anticapsular antibody, leading to early opsonization and facilitation of clearance by the liver. Given the aforementioned histologic features of brain capillaries and the consequent protection of the CSF from blood-borne substances generally, it remains uncertain how the pneumococci and other bacteria traverse these vessels. Some have suggested that microtrauma to the blood-brain barrier is an enhancing mechanism.[9] Further, Scheld and Long have shown in elegant histologic and electron-microscopic studies that when these brain capillaries are incubated in vitro with pneumococci the tight junctions open, forming pores, and intense pinocytotic activity ensues.[10] This phenomenon, however, has not yet been clearly linked with bacterial seeding of the CSF in human meningitis.

Once the organisms gain access to the CSF, host defenses appear completely incapable of controlling rapid growth. In an animal model of meningitis, logarithmic bacterial growth—with a generation time of about 60 minutes—takes place over a 24-hour period until a maximum population density of 100 million bacteria per milliliter is achieved.[11] This rate of growth and clinical characteristics of the disease in cerebrospinal fluid are similar in hematologically normal infected animals (PMNs present) and in those rendered neutropenic by administration of mechlorethamine hydrochloride, a nitrogen mustard (PMNs absent). Polymorphonuclear leukocytes are first seen 14 to 16 hours after infection in healthy animals, and by 24 hours there is a diffuse and intense inflammatory reaction, most pronounced at the base of the brain. This is responsible for cranial nerve palsies often seen in patients with meningitis. Deafness in particular is not an uncommon feature of pneumococcal meningitis. The inflammatory reaction may also lead to thrombosis of the penetrating cerebral vessels—both arterial and venous—and a stroke syndrome may also be encountered. The cerebrospinal fluid protein level begins to rise after 16 to 18 hours and, like bacterial growth, is not influenced by the presence or absence of PMNs. The appearance of serum proteins in the CSF probably results from the opening of the tight junctions of the cerebral capillaries, and complement and antibody gain access to the CSF along with the other serum proteins. The CSF glucose level begins to drop at 14 to 16 hours and it, too, is not influenced by the presence or absence of PMNs. The mechanism of hypoglycorrhachia is in part the result of impaired glucose transport[12] and of increased glucose use by the brain during the tissue

hypoxia produced by the inflammatory response. The increased use relates to associated anaerobic glycolysis, and, indeed, the CSF lactate content increases as glucose content decreases. The specificity of the CSF lactate determination as a diagnostic tool in bacterial meningitis is suspect, however, because other conditions, such as meningeal carcinomatosis or leukemia, result in relatively low CSF glucose and high lactate concentrations through the same mechanism.[13] In the animal model, high CSF lactate levels are associated with a poor prognosis.[14]

The cerebrospinal fluid of the subarachnoid space, the "site" of infection in meningitis, is produced by the choroid plexus in the ventricles of the brain. It circulates through the aqueducts, over the spinal canal and is absorbed through the arachnoid villi into the sagittal sinus system. In all, 500 ml is produced each day, though only about 150 ml circulates at a given moment.[15] This system absorbs CSF by bulk flow, and is also capable of absorbing particles as large as erythrocytes, leukocytes and bacteria directly back into the blood stream. It is not surprising, therefore, that patients who have meningitis will frequently have positive blood cultures because of reabsorption of causative organisms after initial CSF seeding. It has been shown in earlier studies that such organisms, when injected into the CSF directly, first appear in the sagittal sinus of the venous system.[16] One of the well-known sequelae of bacterial meningitis is obstruction of the reabsorptive system, leading to a low-pressure hydrocephalus.[17] In animal models resistance to CSF reabsorption across the arachnoid villous-sagittal sinus membrane in cases of experimental meningitis is greatly increased, a "plugging of the sewer" of the cerebrospinal fluid. In rabbits this resistance lasts for at least 21 days and can be greatly reduced with corticosteroid therapy.[18]

Clinical and Laboratory Presentations

The clinical manifestations of bacterial meningitis have many variations.[19,20] The disease often occurs in a classical epidemiologic setting; this might be a recruit camp or a college dormitory in the case of meningococcal meningitis, or a day-care center in the instance of *H influenzae*. Most cases, however, are sporadic. The presence of impaired host resistance may also be an important historical factor. There is frequently an upper respiratory tract infection preceding the onset of meningitis; outbreaks of adenovirus infections often antedate outbreaks of meningococcal disease and may aid the dissemination of the organism from the nasopharynx or reduce the systemic immune response of the host (or both). Typically, there is an abrupt onset of headache, fever and a stiff neck that may be associated with drowsiness and, on physical examination, a specific resistance to passive neck flexion. Occasionally, back and neck pain or even abdominal distress may predominate. The medical history may reveal clues to certain persons who are susceptible to meningitis, as mentioned above under "Etiology." Neurologic signs are not unusual; seizures or cranial nerve palsies are frequently observed at admission. In a very young patient, irritability, lethargy or poor feeding may be the only finding, whereas in the very old, confusion and occasionally merely a change in personality may be the only manifestation of a bacterial infection in the cerebrospinal fluid.

Therapy must be initiated as quickly as possible once the diagnosis is suspected. If the clinical features are characteristic of meningitis, a lumbar puncture must be done in the emergency room without delay and antibiotics administered promptly thereafter. Imaging studies such as computed tomographic scanning are appropriate before a spinal tap *only* if one cannot safely rule out an intracerebral mass such as tumor, abscess or subdural hematoma. In these cases, we currently recommend initiation of penicillin after obtaining blood specimens for culture; the scan may be done while a patient is receiving this empiric therapy, with lumbar puncture awaiting exclusion of these other diagnoses. Because studies of the animal model have established that the maximum rate at which bacteria can be killed in the CSF by penicillin is about one log an hour, one has the time to carry out such an evaluation without major impact on subsequent cultures of spinal fluid. We do recommend, however, the addition of β-lactamase to the cultured CSF if empiric treatment has been instituted as outlined before the lumbar puncture.

Normal CSF is crystal clear, with turbidity appearing when leukocytes number 200 to 300 per μl; a protein concentration of greater than 150 mg per dl also causes cloudiness independent of cell count. Inspection of the CSF using the Tyndall effect may allow detection of as few as 10 to 50 cells.[21] In cases of meningitis, the opening pressure is usually increased, a result of concomitant cerebral edema. Typically, the protein concentration is high (greater than 100 mg per dl), a phenomenon undoubtedly resulting from alteration in the blood-brain barrier produced by the opening of tight junctions by the organisms. The glucose concentration is usually decreased to less than 30% of the corresponding simultaneous blood glucose, from the aforementioned impairment of transport and anaerobic metabolism. Hypoglycorrhachia is also noted in cases of tuberculosis and occasionally in those of fungal and viral meningitis; similarly, hypoglycemia causes a secondary fall of the CSF glucose level. Cellular analysis of a specimen of CSF usually shows pleocytosis with between 100 and 10,000 leukocytes per μl in which polymorphonuclear leukocytes predominate; occasionally a patient may even have acellular cerebrospinal fluid. A Gram's stain is usually positive (80%), and bacterial cultures are diagnostic in 70% to 85%. Meningococcal and *Listeria* organisms are the most apt to be missed on Gram's stain. Pretreatment with antibiotics also can give rise to negative cultures and influence the cell count; in such cases, an empiric course of appropriate antimicrobial therapy (see below) must be administered solely on the basis of high clinical

suspicion. Antigen-detection tests (such as counterimmunoelectrophoresis), though highly specific, are of variable sensitivity and are most useful in those instances wherein pretreatment may negate cultures. The cost of the test and the shelf-life of reagents indicate that this may be effectively used only in hospitals with a large number of possible cases of meningitis. Finally, there is some interest in CSF lactate in diagnosis but, as discussed above, this is not specific for meningitis.

Another clinical conundrum is the approach to a patient with meningitis deemed clinically to be viral; such persons may have neutrophilic pleocytosis in the cerebrospinal fluid early in the course of the illness, though the total cell count is less than 1,000, with fewer than 50% PMNs. Because the cell count varies greatly in bacterial meningitis, withholding antibiotics may be justified only when a patient is clinically well. In such instances a reexamination of a CSF specimen in 6 to 12 hours will show the expected lymphocytic predominance.[22] The decision to use antibiotics is a clinical one in this setting, and any error should be in the direction of treatment rather than observation.

Antimicrobial Therapy

Penicillin remains the drug of choice for most causes of meningitis in adults. It should be given intravenously in high dosages (12 to 20 million units a day) for ten days to two weeks, though there are no studies establishing proper duration of therapy. For meningococcal and pneumococcal meningitis, chloramphenicol is still a sound alternate choice for patients allergic to penicillin. If the clinical response is gratifying, there is no need for repeat lumbar puncture.

The new third-generation cephalosporins appear to have an important contribution to make in the treatment of some forms of bacterial meningitis. Historically, the cephalosporins have a poor record in the treatment of meningitis. Cephalothin sodium and cephaloridine were shown to be inadequate therapy for pneumococcal and meningococcal meningitis, and later cefamandole was shown to be ineffective for treating *H influenzae* meningitis. Cefotaxime sodium and moxalactam disodium, however, more effectively penetrate into the CSF and produce drug concentrations there at least 10 to 20 times greater than the minimum bactericidal concentration for *H influenzae* and many of the Gram-negative enteric organisms. In a recent study, 30 patients who had meningitis (25 with *H influenzae* and 5 with meningococcal disease) were given moxalactam. Mean CSF concentrations one to two hours after parenteral administration approached 15 μg per ml, whereas the concentration required to kill the organism was less than 0.25 μg per ml. There was a cure rate of 96% in this patient population.[23] Others have reported similar results and it may now be time to use one of these drugs for the treatment of *H influenzae*[24,25] meningitis rather than the combination of chloramphenicol/ampicillin currently recommended, with its potential toxicity and clinical antagonism of drug action.[26] Both cefotaxime and moxalactam are active against β-lactamase-producing *H influenzae*. The activity of moxalactam against the Gram-positive organisms in CSF is not adequate to recommend its use; several cases of pneumococcal meningitis have been reported in patients actually receiving moxalactam. One would also not use this drug in neonates with group B streptococcal meningitis or in patients with *Listeria monocytogenes* disease. Cefotaxime may be effective against pneumococcal meningitis; studies in Europe suggest its possible value in this disease. However, it also has no activity against *L monocytogenes*. Thus, in purulent meningitis in adults in whom *Listeria* or a Gram-negative bacillary cause cannot be excluded on initial assessment, a combination of penicillin and moxalactam is a logical choice. Ceftriaxone sodium, a new drug that has a very long half-life, appears to have excellent activity against the common meningeal pathogens —except *L monocytogenes*—and it achieves very high CSF concentrations. Several teams are currently investigating it for the treatment of meningitis and the drug may prove to be of considerable value in the future.

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